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Synthesis of Cytotoxic Sinapyl Alcohol Derivatives from*Ligularia nelumbifolia*

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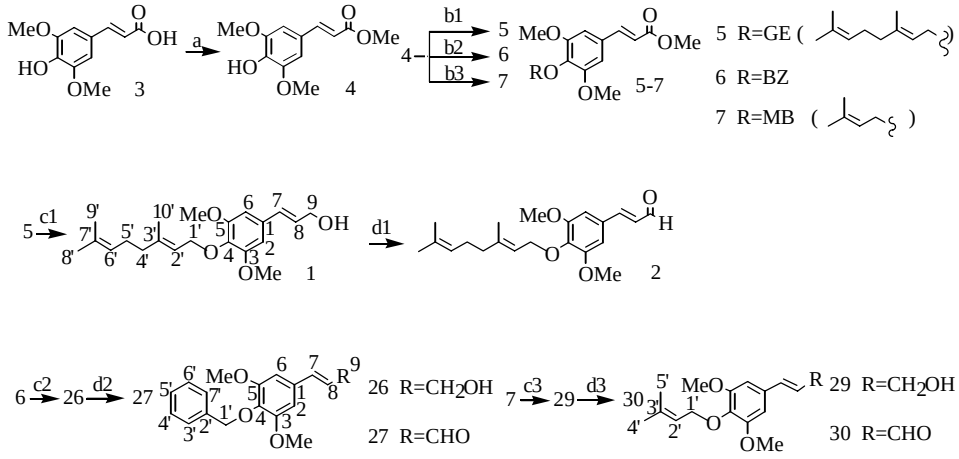
Abstract: Total synthesis of two cytotoxic natural products, nelumol A (**1**) and nelumal A (**2**), were carried out by two different paths. 4-O-Benzyl substitute analogues **26** and **27**, as well as the 4-O-(2-methyl-butenyl) derivatives **29** and **30** were also synthesized for a SAR investigation. **1** and **2** were also measured on different tumor cell line.

Keywords: Natural products, cytotoxicity, total synthesis, SAR, pharmaceutical chemistry, sinapyl alcohol derivatives.

Ligularia nelumbifolia has been used as folk medicines for pulmonary tuberculosis and apoplexy[1]. Previous phytochemical examination on *Ligularia* species found mainly eremophilane derivatives[2]. Interestingly, only several sinapyl alcohol derivatives and aromatic components were isolated in this species[3]. Very recently, two main principles of this species, nelumol A (**1**)[3,4] and nelumal A (**2**) were found to be cytotoxic to KB cell (**Table 1**)[5]. This urged our interest to synthesize **1** and **2** for further constructing the structure-activity relationship concept.

The first path could begin with commercial available acid **3**. After protection of the carboxylic acid to **4**, Mitsunobu reaction of the methyl ester **4** with geranyl alcohol afforded **5**[6]. Reduction of **5** by DIBAH afforded quantitatively nelumol A **1**, while oxidation of **1** by magnesium dioxide will conveniently give nelumal A **2** in 92% yield (**Scheme 1**).

Scheme 1



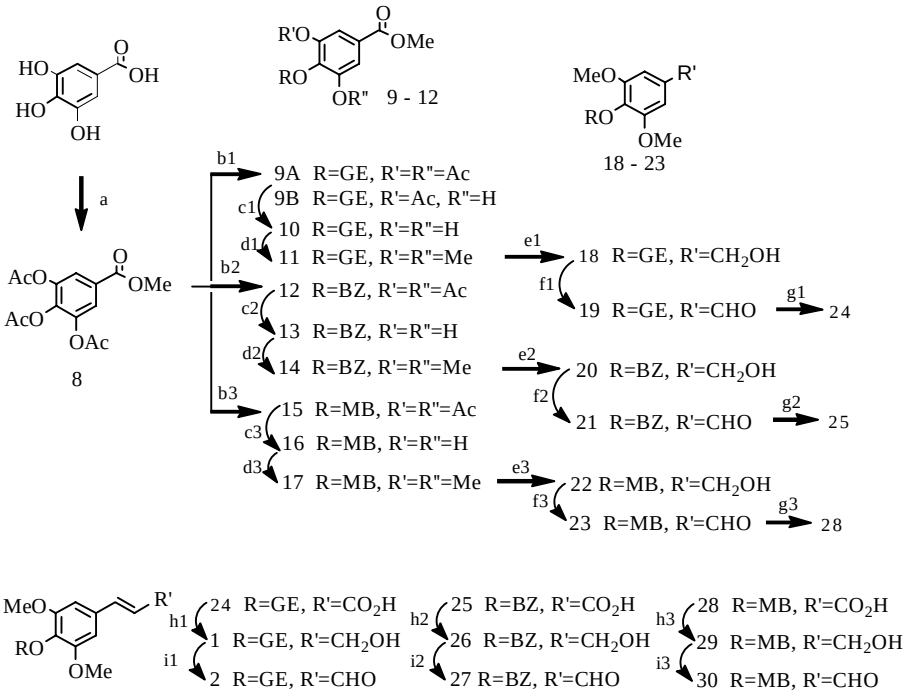
(a) H_2SO_4, MeOH, reflux, 2 h, 98%; (b1) geranyl alcohol, Ph_3P, DEAD, 24 h, 50%; (b2) benzyl alcohol, Ph_3P, DEAD, 24 h, 65%; (b3) 2-methylbutenol, Ph_3P, DEAD, 24 h, 60%; (c1) DIBAH, THF, -78^{0}C, 2 h, 86%; (c2) ibid, 88%; (c3) ibid, 80%; (d1) 1: PCC, CH_2Cl_2, rt, 6 h, 81%; 2: MnO_2, EtOAc, rt, 92%; (d2) 1: PCC, CH_2Cl_2, rt, 6 h, 83%; 2: MnO_2, EtOAc, rt, 92%; (d3) 1: PCC, CH_2Cl_2, rt, 6 h, 81%; 2: MnO_2, EtOAc, rt, 94% (GE=geranyl, BZ=benzyl, MB = 2-methylbutenyl)

Another path could be carried out from gallic acid (**Scheme 2**). Methylation of the carboxylic acid afforded methyl gallate in 96% yield. Protection of three phenolic hydroxyls by acetoxy groups, and the product **8** was subjected to a selective substitution reaction, during which the 4-acetoxy group was replaced by a geranyl moiety[7]. Thus **9** (including **9A** & **9B**) was formed. The by-product **9B** could also be transformed to **10**. Following by deacetylation under basic methanol solution, the phenolic hydroxy groups could be transformed to a methoxy group derivative **11** (82% yield in two steps). Reduction of **11** by LAH afforded the primary alcohol **18**, which could be oxidized to aldehyde **19** by pyridinium chlorochromate in 86% yield. The aldehyde **19** was condensed with malonic acid in basic environment under the catalysis of piperidine, thus afford the *E*-form olefinic conjugated acid **24**. Reduction of the acid by LAH afforded, apart from the 80% yield of the expected target molecule **1**, 7, 8-hydrogenated primary alcohol as a by-product in 5% yield. Finally, nelumal A **2** could be obtained by manganese dioxide oxidation in 92% yield. The total yield of **Scheme 2** is 28%, 11 percents lower than that of **Scheme 1**. The pharmacological screening of synthetic **1** and **2** were performed further on several other models and the results are shown in **Table 1**.

To examine the importance of the C-4 side chain on cytotoxicity, we designed another target molecular **26**, which possesses an aromatic benzyl group attached to C-4 oxygen. Furthermore, a five-carbon side chain was also introduced to the skeleton to construct the SAR concept. Two paths were examined to synthesize these analogues, which were shown in **Scheme 1** and **2**. Cytotoxicity screening of these analogues are

shown in **Table 2**.

Scheme 2



(a) 1: H_2SO_4, MeOH, reflux, 2 h, 96%; 2: Ac_2O, Py, rt, 12 h, 93%; (b1) geranyl bromide, DMF, 0°C, 24 h, 50% of 9A, 29% of 9B; (b2) benzyl bromide, DMF, 0°C, 24 h, 67%; (b3)2-methylbutenyl bromide, DMF, 0°C, 24 h, 60%; (c1) K_2CO_3, MeOH-H_2O, rt, 0.5 h, 90%; (c2) ibid, 88%; (c3) ibid, 86%; (d1) MeI, K_2CO_3, reflux, 3 h, 91%; (d2) ibid, 94%; (d3) ibid, 89%; (e1) LAH, ether, 0°C, 90%; (e2) ibid, 94%; (e3) ibid, 91%; (f1) PCC, CH_2Cl_2, rt, 6 h, 86%; (f2) ibid, 88%; (f3) ibid, 89%; (g1) malonic acid, piperidine, Py, reflux, 4 h, 86%; (g2) ibid, 90%; (g3) ibid, 88%; (h1) LAH, ether, 0°C, 80%; (h2) ibid, 86%; (h3) ibid, 85%; (i1) MnO_2, EtOAc, rt, 2 h, 92%; (i2) ibid, 95%; (i3) ibid, 90% (GE=geranyl, BZ=benzyl, MB=2-methylbutenyl)

Table 1 IC_{50} of **1** and **2** on some selected pharmacological models (mol/L)

	NMDA receptor [^{3}H]MK-801	Collagenase-1	A-549 cell	HL-60 cell
1	6.6×10^{-5}	4.0×10^{-4}	3.4×10^{-5}	6.7×10^{-6}
2	4.6×10^{-6}	3.4×10^{-4}	2.2×10^{-5}	1.2×10^{-5}

Table 2 IC_{50} of compounds **1**, **2**, **26**, **27**, **29**, **30** on KB cell (mol/L)

1	**2**	**26**	**27**	**29**	**30**
2.6×10^{-6}	3.0×10^{-6}	8.6×10^{-4}	6.4×10^{-4}	7.8×10^{-6}	5.3×10^{-6}

It could be seen that compounds **26** and **27** are less cytotoxic to KB cell, while the five-carbon side chain derivatives **29** and **30** own similar cytotoxicities to KB cell with those of **1** and **2**. Thorough examinations of SAR concept are in progress.

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